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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
MYERS, C	
ART UNIT	**PAPER NUMBER**
1655	3

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/782,386	Applicant(s) WOOD ET AL.	
	Examiner Carla Myers	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821(e) which states that "(t)the computer readable form is a copy of the "Sequence Listing" and will not necessarily be retained as part of the patent application file. If the computer readable form of a new application is to be identical with the computer readable form of another application of the applicant on file in the Office, reference may be made to the other application and computer readable form in lieu of filing a duplicate computer readable form in the new application. The new application shall be accompanied by a letter making reference to the other application and computer readable form...". Accordingly, Applicant is required to submit a letter stating, for example:

The computer readable form in this application is identical with that filed in Application Number _____, filed _____. In accordance with 37 CFR 1.821(e), please use the (first-filed, last-filed or only, whichever is applicable) computer readable form filed in that application as the computer readable form in the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the computer readable form that will be used for the instant application. A paper copy of the Sequence Listing is (included in the originally-filed specification of the instant application, included in a separately filed preliminary amendment for incorporation into the specification, whichever is applicable).

Furthermore, Applicant is required to submit a paper copy of the Sequence Listing and a letter stating that the content of the paper and computer readable copies of the Sequence Listing are the

same and, where applicable, include no new matter. In addition, the specification should be amended to include the appropriate sequence identifiers next to each sequence recited.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cimino (U.S. Patent No. 5,652,096).

Cimino teaches methods for detecting the presence of a mutation in a target nucleic acid and for discriminating between fully complementary and partially complementary duplexes formed between a probe and a target nucleic acid (col. 5). In the method of Cimino, a probe comprising a photoactivatable cross-linking agent is combined with a target nucleic acid under mild hybridization conditions, the resulting complexes are irradiated to form cross-links between the probe and the target nucleic acid, the cross-linked nucleic acids are separated by denaturing polyacrylamide gel electrophoresis, and the migratory pattern of the cross-linked nucleic acids are analyzed to distinguish between cross-linked nucleic acids which are fully complementary and cross-linked nucleic acids

having one or more mismatches (see, for example, col. 7-11). Cimino states that denaturing gel electrophoresis allows one to distinguish between crosslinked homoduplexes and crosslinked heteroduplexes such that probe:mutant target is retarded in the gel and runs above the probe:normal target complex (col. 10). Cimino exemplifies methods using control standards having known mutant and normal target sequences (e.g., col. 11) and methods in which target nucleic acid is obtained from a patients blood sample (col. 15). In the later example, Cimino teaches including controls in which the sample is not irradiated and markers consisting of unmodified probe. Cimino does not specifically exemplify methods in which a standard is included which consists of a known mismatched or matched cross-linked doubled-stranded DNA. However, at the time the invention was made the inclusion of control standards on electrophoresis gels was well known in the art and it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cimino so as to have included control standards consisting of a known mismatched or matched cross-linked doubled-stranded DNA in the electrophoresis gel in order to have assured accurate evaluation of the migration pattern of the target sample:probe duplexes and thereby to have increased the overall accuracy of the detection method.

With respect to claims 2 and 8 Cimino teaches that the probe may be labeled, particularly with a radioactive moiety (col. 15, line 23). With respect to claims 3 and 7, Cimino (e.g., col. 9-10) teaches that the sample nucleic acid is prepared by PCR and may be labeled with a detectable moiety. In reference to claims 5-10, Cimino teaches irradiation of the target-probe complexes at 320-400 nm (col. 8). Cimino exemplifies methods in which the probe is a 16 mer and the target nucleic acid is

a 31 mer (col. 10). Furthermore, in the examples provided therein, a variety of hybridization conditions are utilized (col. 10), including mild hybridization conditions, with the temperature of hybridization ranging from 4 to 40°C. It is stated (col. 6) that, as with conventional hybridization techniques, discrimination of complete or partial complementarity is a function of temperature. It is further stated that "(a)t equilibrium and above the melting temperature of the probe:mutant target complex, there is a strong preference for the probe to bind preferentially to the normal target" (col. 11). Cimino exemplifies methods in which hybridization is performed using tetramethylammonium chloride in the hybridization solution. Cimino does not teach using hybridization solutions containing sodium chloride and/or does not particularly state that the conditions of hybridization are of a particular level of stringency. However, it was conventional in the art of molecular biology to perform hybridization reactions in the presence of sodium chloride and the reaction parameters which affect hybridization specificity, including salt molarity, temperature, and degree of complementarity between probe and target, were well known in the art at the time the invention was made. To determine the optimum concentration of reactants is considered to be well within the skill of the art (In re Kronig 190 USPQ 425). Accordingly, it would have been obvious to one of ordinary skill in the art and well within the skill of the art at the time the invention was made to have modified the method of Cimino so as to have utilized an effective molarity of sodium and to have modified the temperature of hybridization according to the length of the probe and salt concentration in order to have provided for the optimum formation of hybridization duplexes formed between the probe and

target nucleic acid and/or optimum discrimination between the probe:mutant and probe:normal nucleic acid duplexes.

3. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cimino (U.S. Patent No. 5,652,096), as applied to claims 1-5 and 7-10 above, in view of Saba (U.S. Patent No. 5,082,934).

Cimino teaches the introduction of a photoactivatable cross-linking agent into the probe and exemplifies the use of the cross-linking agent methoxypsoralen. Cimino also states that the presence of the crosslinking reagent on the probe does not affect the specificity of base pairing (col. 7). Cimino does teach using a crosslinking agent which comprises a coumarinyl group.

Saba (col. 12) taches the introduction of coumarinyl groups into oligonucleotide probes and states that the oligonucleotide probes comprising coumarinyl crosslinking groups specifically hybridize with target nucleic acids and are effectively crosslinked, following photoactivation, with target nucleic acids.

In view of the disclosure of Saba, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cimino so as to have used a coumarinyl crosslinker in place of methoxylpsoralen because this would have provided an equally effective crosslinker which allowed for specific hybridization and crosslinkage of the probe to target nucleic acids.

4. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cimino (U.S. Patent No. 5,652,096), as applied to claims 1-5 and 7-10, above, in view of Campbell (EP 0329 311).

Cimino teaches that the target nucleic acid "can be from any source, whether synthesized, cloned or naturally occurring, as long as they contain some part of the sequence of interest (col. 8). Cimino further teaches performing PCR to generate the target nucleic acids so that the position of the mismatch relative to the crosslinking site can be specifically chosen. Cimino does not teach generating the target nucleic acid by restriction enzyme digestion.

Campbell teaches a method for detecting the presence of a mutation in a target nucleic acid wherein target nucleic acid is hybridized with a probe and the resulting duplex is analyzed for the presence of a base pair mismatch. In particular, Campbell teaches that the target nucleic acid is generated by restriction enzyme digestion (see, for example, page 10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cimino so as to have generated the target nucleic acid by restriction enzyme digestion, as taught by Campbell, because this would have provided an equally effective and rapid means for generating smaller fragments of the target nucleic acid that would be of a suitable length for hybridization to the probe and would have also provided an equally effective means for controlling the position of the potential mismatch in the target nucleic acid relative to the crosslinking site.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,187,532. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '532 are inclusive of methods of detecting the presence or absence of a mismatch between a probe and a nucleic acid target wherein said probe comprises a known nucleotide sequence and a cross-linking agent wherein said methods comprise hybridizing a probe to a target nucleic acid sample in a hybridization medium, irradiating the medium to form cross-links between said probe and target nucleic acid when said probe and target nucleic acid are hybridized to generate cross-linked double-stranded nucleic acids, separating the nucleic acids by electrophoresis and comparing the migratory rate of the cross-linked double-stranded nucleic acid to a standard in order to identify the presence of at least one mismatch. It is noted that the instant claims are broadly drawn to methods which utilize probes comprising any type of cross-linking agent, and thereby are inclusive of the methods of '532 which require the use of a sugar-free, base-free photoactivatable cross-linking coumarinyl glycerol group.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for this Group is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Carla Myers

July 23, 2001

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER